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Cu(I)-catalysed chemo-, regio-, and stereoselective radical 1,2-carboalkynylation with two different terminal alkynes

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Transition-metal-catalysed asymmetric multicomponent reactions with two similar substrates often suffer from the lack of strategies to control the chemo-, regio-, and stereoselectivity of these substrates due to the close similarity in the chemical structures and properties of each reagent. Here, we describe a Cu(I)-catalysed asymmetric radical 1,2-carboalkynylation of two different terminal alkynes and alkyl halides with high chemo-, regio-, and stereoselectivity by using sterically bulky chiral tridentate anionic *N,N,P*-ligands and modulating alkynes with different electronic properties to circumvent above-mentioned challenges. This method features good substrate scope, high functional group tolerance of two different terminal alkynes, and diverse alkyl halides, providing universal access to a series of useful axially chiral 1,3-enyne building blocks.

Multicomponent reactions have been identified as a prominent strategy for the rapid generation of molecular complexity[1–6]. The key to the success of multicomponent reactions is to meticulously ensure the compatibility of each step, allowing the simultaneous addition of all reactants and catalysts at the onset of the reaction. Among numerous processes, transition-metal-catalyzed asymmetric multicomponent radical reactions have gained considerable interest due to their remarkable compatibility with many functional groups and unique reactivity profile[7–15]. To ensure high levels of chemo-, regio-, and enantioselectivity, one variant of this process is to combine reactants possessing different reactivities (Fig. 1a, left). Another type of reaction is to utilize easily available reactants with close similarity in the chemical structures and properties (Fig. 1a, right). The similarity would undoubtedly increase the complexity of reaction pathway, making it difficult to achieve a delicate balance among chemo-, regio-, and stereoselectivity.

Conjugated 1,3-enynes are important structural units in organic synthesis, serving as precursors for polysubstituted aromatic rings, biologically active molecules, and organic materials[16–19]. Although many strategies have been developed for the construction of 1,3-enynes[20–29], the direct coupling of alkynes to 1,3-enynes via a radical relay pathway has been rarely reported[30–34]. In this context, Wu[30], Koenigs[31], and others[32] have reported the Pd-catalyzed dicarbofunctionalization of terminal alkynes using secondary or tertiary alkyl iodide, including radical Mizoroki−Heck reactions for the synthesis of 1,3-enynes. Nishikata and co-workers demonstrated a copper-catalyzed tandem radical addition/Sonogashira-coupling process using alkyl bromides and terminal alkynes[33]. However, the limitation of the above processes stems from the use of the same alkyne in both steps of the tandem process, which ultimately results in the installation of two identical substituents on the enyne motifs. To increase the diversity of 1,3-enynes, the Koh group made a breakthrough using structurally different bromoalkynes as the coupling partners to achieve the 1,2-carboalkynyaltion of terminal alkynes[34]. Despite these impressive advances, the development of a catalytic version of two

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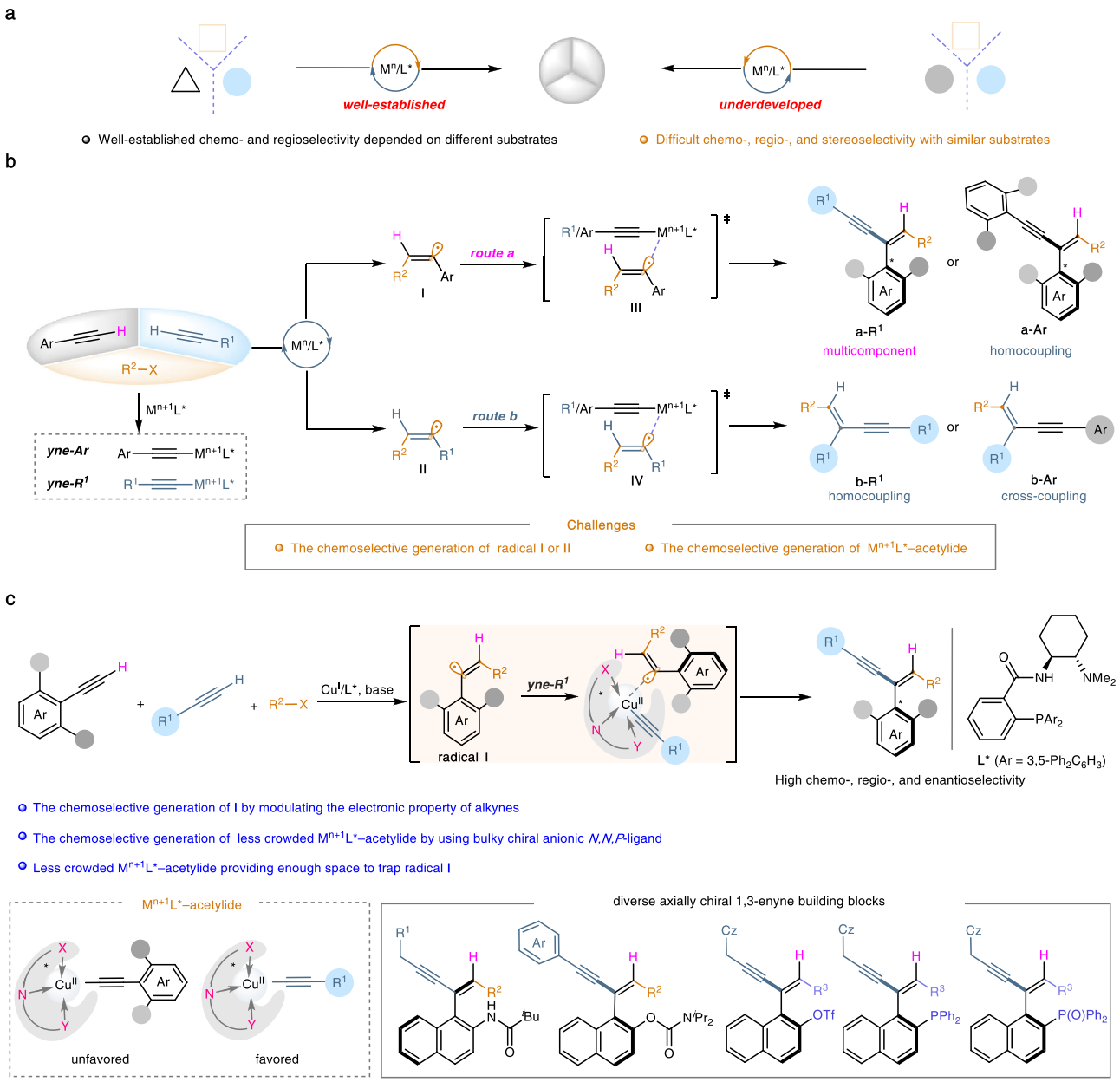

Fig. 1 | Motivation and development of Cu(I)-catalyzed enantioselective radical 1,2-carboalkynylation of two different terminal alkynes. a Transition-metal catalyzed three-component asymmetric radical reactions. **b** Challenges for asymmetric radical difunctionalization of two different terminal alkynes. **c** Cu(I)-catalyzed enantioselective radical 1,2-carboalkynylation with two terminal alkynes. M metal, ^{t}Bu *tert*-butyl, Ar aryl, ^{i}Pr isopropyl, Tf trifluoromethanesulfonyl, Cz carbazolyl.

similar terminal alkynes to realize highly chemo- and regioselective control is still challenging. Moreover, despite the recent enormous development of radical asymmetric catalysis[35–52], the enantioselective radical difunctionalization of two different terminal alkynes with simple radical precursors to give the axially chiral 1,3-enyne frameworks[53–82] remains unexploited (Fig. 1b). In addition to innate reactions of terminal alkynes and alkyl halides, such as Glaser-homocoupling[83–85], halogen atom transfer reaction[22,86–89], and Sonogashira-coupling[90–92], this reaction suffers from additional challenges: (1) how to achieve the chemoselectivity between vinyl radical **I** and **II**, which are generated from the two terminal alkynes[93–97] (Fig. 1b); (2) how to ensure the chemo-, and stereoselectivity in the coupling of vinyl radical with the M^{n+1}**L***–acetylide complex (Fig. 1b, **yne-Ar** and **yne-R^1**). Therefore, developing a new strategy to synthesize axially chiral 1,3-enynes with high chemo-, regio-, and stereoselectivity is urgently needed. To address these challenges, we expected to chemoselectively control the vinyl radical generation to give radical **I** by regulating the electronic properties of two different terminal alkynes (Fig. 1b, route a). We anticipated that our recently developed copper catalysts with steric crowded chiral multidentate anionic ligands[91,92,98–106], could selectively promote deprotonation of alkyne with smaller substitute **R^1** to generate less steric crowded M^{n+1}**L***–acetylide complex **yne-R^1**. At the same time, the thus-generated **yne-R^1** intermediate with low steric congestion might also prefer to trap vinyl radical **I**, therefore not only controlling the desired asymmetric process[91,98–103] but also overcoming the readily occurring side reactions to afford axially chiral 1,3-enynes with high chemo-, regio-, and stereoselectivity.

Herein, we report a copper-catalyzed three-component asymmetric radical 1,2-carboalkynylation using two different terminal alkynes, providing a straightforward route to a diverse array of axially chiral 1,3-enynes (Fig. 1c). This protocol exhibits excellent chemo-,

regio-, and stereoselectivity under mild conditions, featuring a broad substrate scope of readily available terminal alkynes and high functional group tolerance, enabling the synthesis of a variety of axially chiral 1,3-enynes. Furthermore, the reaction could be scaled up, and the resulting axially chiral 1,3-enynes could be easily transformed into a series of useful axially chiral 1,3-enyne building blocks.

Results

Reaction development

To examine our aforementioned proposal, aryl alkyne **S1** with a large 2-substitutent was selected as the model coupling alkyne, therefore hoping not only to generate the conjugation-stabilized vinyl radical but also to introduce axial chirality. Alkyl alkyne **S16**, which lacked conjugation effect and would generate thermodynamically unfavorable vinyl radical, was used as the nucleophile to construct 1,3-enyne skeletons. Also, copper salts with chiral ligands would undergo single-electron transfer (SET) with *tert*-butyl α-bromoisobutyrate **C1** to initiate this reaction, giving rise to the alkyl radical. At first, a screening of bidentate neutral ligands, such as bisoxazoline-based ligand **L*1** and phosphinooxazoline ligand **L*2**, with CuTc as the catalyst, indicated no reaction activity, presumably due to the insufficient reducing capability of the copper complex (entries 1–2; Table 1). Thus, we tested chiral anionic oxazoline-derived *N,N,N*-ligand **L*3**, which have shown enough reducing capability of copper catalyst to reduce tertiary alkyl bromide in our previous report[104,105]. Indeed, the desired product **1** was obtained in 28% yield, albeit with low enantioselectivity (10% e.e.) along with the homocoupling side product **1'** in a higher yield than **1**, and 14% yield of atom transfer side product **1''** (entry 3, and also see Supplementary Table 3), demonstrating the competence of the *N,N,N*-coordination manifold in promoting the desired reaction. Interestingly, the reaction using the cinchona alkaloid-derived tridentate picolinamide **L*4**[106] still suffered from alkyne homocoupling. To our surprise, tridentate *N,N,P*-tridentate ligand **L*5**[91,107], gave the desired product **1** in 56% e.e., albeit with low yield while inhibiting the alkyne homocoupling process (entry 5). Encouraged by this finding, we next examined the other steric bulk *N,N,P*-tridentate ligand **L*6** and found that the reaction provided product **1** in 77% e.e. but the reaction efficiency remained low (entry 6). Accordingly, we next sought to install a sterically bulky 3,5-disubstituted phenyl ring in **L*7**, and the e.e. increased to 87% (entry 7). Replacing the key chiral skeleton with cyclohexylenediamine of **L*8** significantly improved the yield of **1** to 75% with enhanced enantioselectivity (89% e.e.) with excellent chemo- and regioselectivity. Collectively, these results indicated that the use of bulky *N,N,P*-tridentate ligand **L*8** is crucial for not only selectively generating less steric Cu^{I}**L***–acetylide complex through deprotonation of smaller-sized alkyne **S16** but also effectively interacting vinyl radical **I** with thus-generated Cu^{I}**L***–acetylide complex due to low steric congestion, which would exert effective cross-coupling to give **1** while inhibiting side self-coupling and atom transfer processes. Further optimization of conditions, including copper salts, bases, solvents, reaction time and other factors (see Supplementary Tables 1–7 for the results of condition screening), identified the optimal conditions (entry 9) as follows: **S1** (2.0 equiv.), **C1** (2.0 equiv.) and **S16** (0.05 mmol, 1.0 equiv.) in the presence of CuTc (10 mol%), **L*8** (12 mol%), and Cs_2CO_3 (5.0 equiv.) in Et_2O at 10 °C for 5 days under argon. This condition provided **1** in 72% yield and 93% e.e. with excellent chemo- and regioselectivity.

Substrate scope

Considering the high utility of axially chiral phenol compounds[108,109], we first investigated the reaction with 2-oxyaryl alkynes, and those bearing a wide range of functional groups with different electronic properties were readily accommodated in this reaction. As for the scope of 2-oxyaryl alkynes, a series of 6-substituted naphthyl rings were readily accommodated in this reaction (**2**–**5**; Fig. 2a). However, 6- and 7-phenyl-subsituted aryl alkynes suffered from a low conversion to afford the desired products **3** and **6** in low yield, likely due to steric hindrance of the phenyl substituent. Furthermore, various 4- and/or 5-substituted naphthyl rings underwent the reaction smoothly, delivering the corresponding products **7**–**9** in 62–70% yield with 91–92% e.e. Likewise, good tolerance of 5- and/or 6-substitution of 2-oxyphenyl alkyne substrates was also observed (**10** and **11**). In addition, 4,6-disubstituted 2-oxyphenyl alkyne was also applicable to this reaction, affording good enantioselectivity and high yield (**12**). As for the other *ortho-oxygen*-substituted alkynes, such as carboxylic, proved to be workable in this reaction, providing the desired products (**13** and **14**) with high enantioselectivity and moderate yield. However, for *ortho-nitrogen*-substituted groups like pivaloyamine, the corresponding products **15** was obtained with decreased enantioselectivity under the standard reaction conditions. To further improve enantioselectivity, after systematic optimization efforts (see Supplementary Table 8 for condition optimizations), we found that the more sterically hindered cinchona alkaloid-derived *N,N,P*-**L*11** was able to control enantioselectivity, affording the final product **15** with 70% yield and 86% e.e. (Fig. 2b). As for the *ortho-carbon*-based alkynes, such as phenyl (**S28**) and isopropyl (**S29**), the desired products **P1** and **P2** were obtained with low yield and e.e. (see Supplementary Fig. 4). These results demonstrated the crucial role of the oxygen- and nitrogen-containing functional groups at the *ortho* positions. The *ortho*-$(O)PPh_2$ substituted alkyne **S30** failed to afford the desired product possibly due to the catalyst poisoning by the diphenyl phosphine oxide group (see Supplementary Fig. 4).

We then turned our attention to the scope of radical precursors (Fig. 3a). Numerous α-bromo alkyl and aryl esters including ethyl (**C2**), cyclopentyl (**C3**), 4-methoxybenzyl (**C4**), and tolyl (**C5**) were effective for the reaction to deliver the corresponding products **16**–**19** with good efficiency and stereoselectivity. Furthermore, the cyclic α-bromoesters (**C6**) also participated readily in the reaction, producing **20** in moderate yield and excellent enantioselectivity. In addition, tertiary alkyl bromides with α-amide functional group exhibited good reactivity to produce **21** in 78% yield with 99% e.e. It's worth noting that the Weinreb amide-type bromide **C8** was also compatible with the reaction, affording **22** in 30% yield with 92% e.e. However, tertiary α-bromo ketone failed to give the desired product (see Supplementary Fig. 5). In addition, primary and secondary alkyl bromides, such as (bromomethyl)benzene, ethyl 2-bromoacetate, 2-bromoacetonitrile, (3-bromoprop-1-yn-1-yl)trimethylsilane, (bromomethylene)dibenzene, and diethyl 2-bromomalonate as well as Togni reagent, and tosyl chloride were not suitable for the reactions (see Supplementary Fig. 5 for more details). We then proceeded to investigate the scope of alkyne nucleophiles. Regarding the alkyne scope, many alkyl alkynes with aliphatic chains or a variety of functional groups, such as ester (**23**), ether (**24**), benzyloxy (**25**), *p*-toluenesulfonyloxy (**26**), carbamate (**27**) as well as phenylamine (**28**), underwent the reaction smoothly to generate **23**–**28** in moderate to good yield with excellent chemo-, regio- and enantioselectivity. Notably, the low yield of **25**–**27** is due to the low conversion of the corresponding alkyl alkynes.

Unlike alkyl alkynes, aryl alkynes appeared to be more similar to **S1** in chemical properties, which should pose a greater challenge in controlling the chemo-, regio-, and stereoselective. Based on radical polarity properties[96,97], we proposed that tuning the electronic properties of two similar terminal alkynes may influence the chemoselectivity of the radical addition, in which in-situ generated electrophilic tertiary alkyl radical from α,α-dimethyl-α-bromoesters would easily prefer to attack aryl alkyne **S1** than more electron-withdrawing aryl alkynes. In order to realize such transformation with excellent selectivity, aryl alkynes bearing diverse electron-withdrawing groups (chloride, methoxycarbonyl, trifluoromethyl, and cyano) on the phenyl rings were selected as the nucleophile. Indeed, the reaction worked smoothly to afford the corresponding products **29**–**32** in 40–58% yield with 80–83% e.e. (Fig. 3b). Furthermore, heteroaryl alkyne featuring pyridine (**33**) was suitable

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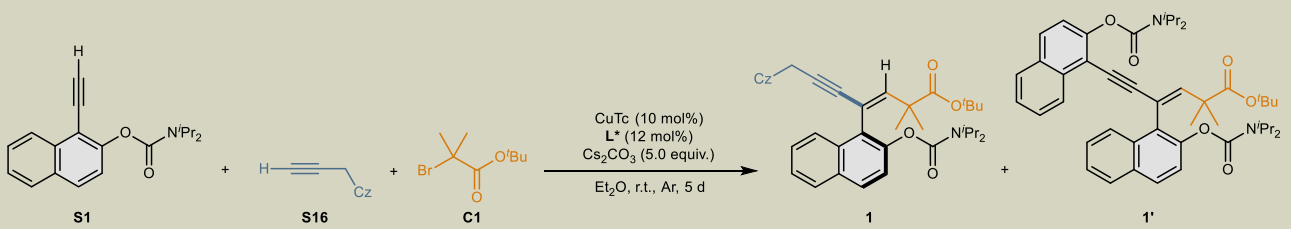
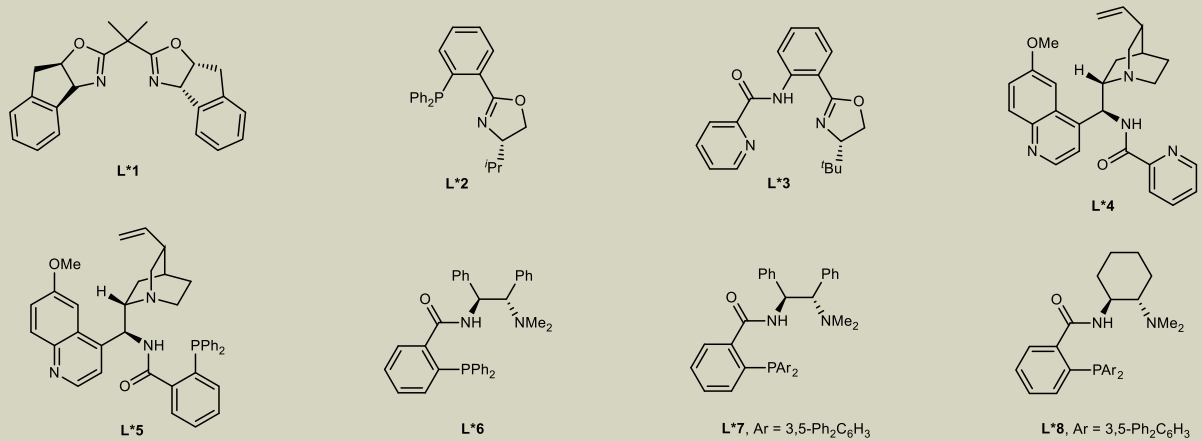
Table 1 | Effect of chiral ligands





Entry	L*	Yield of 1/%	E.e. of 1/%	Yield of 1'/%
1	**L*1**	0	–	0
2	**L*2**	0	–	0
3[a]	**L*3**	28	–10	36
4	**L*4**	44	10	31
5[b]	**L*5**	10	56	Trace
6	**L*6**	11	77	Trace
7	**L*7**	24	87	Trace
8	**L*8**	75	89	Trace
9[c]	**L*8**	72	93	Trace

Reaction conditions: **S1** (2.0 equiv.), **C1** (2.0 equiv.), **S16** (0.05 mmol, 1.0 equiv.), CuTc (10 mol%), **L*** (12 mol%), and Cs_2CO_3 (5.0 equiv.) in Et_2O (1.0 mL) at r.t. for 5 d under argon. Yield of **1** and **1'** was based on ^1H NMR analysis of the crude products using dibromomethane as an internal standard; E.e. values of **1** were based on chiral HPLC analysis. [a]with 14% yield of atom transfer side product **1''**. [b]with 10% yield of **1''**. [c]at 10 °C. **L***, chiral ligand; Et_2O, diethyl ether; CuTc, Copper(I) thiophene-2-carboxylate; r.t., room temperature; e.e., enantiomeric excess; Ar, argon.

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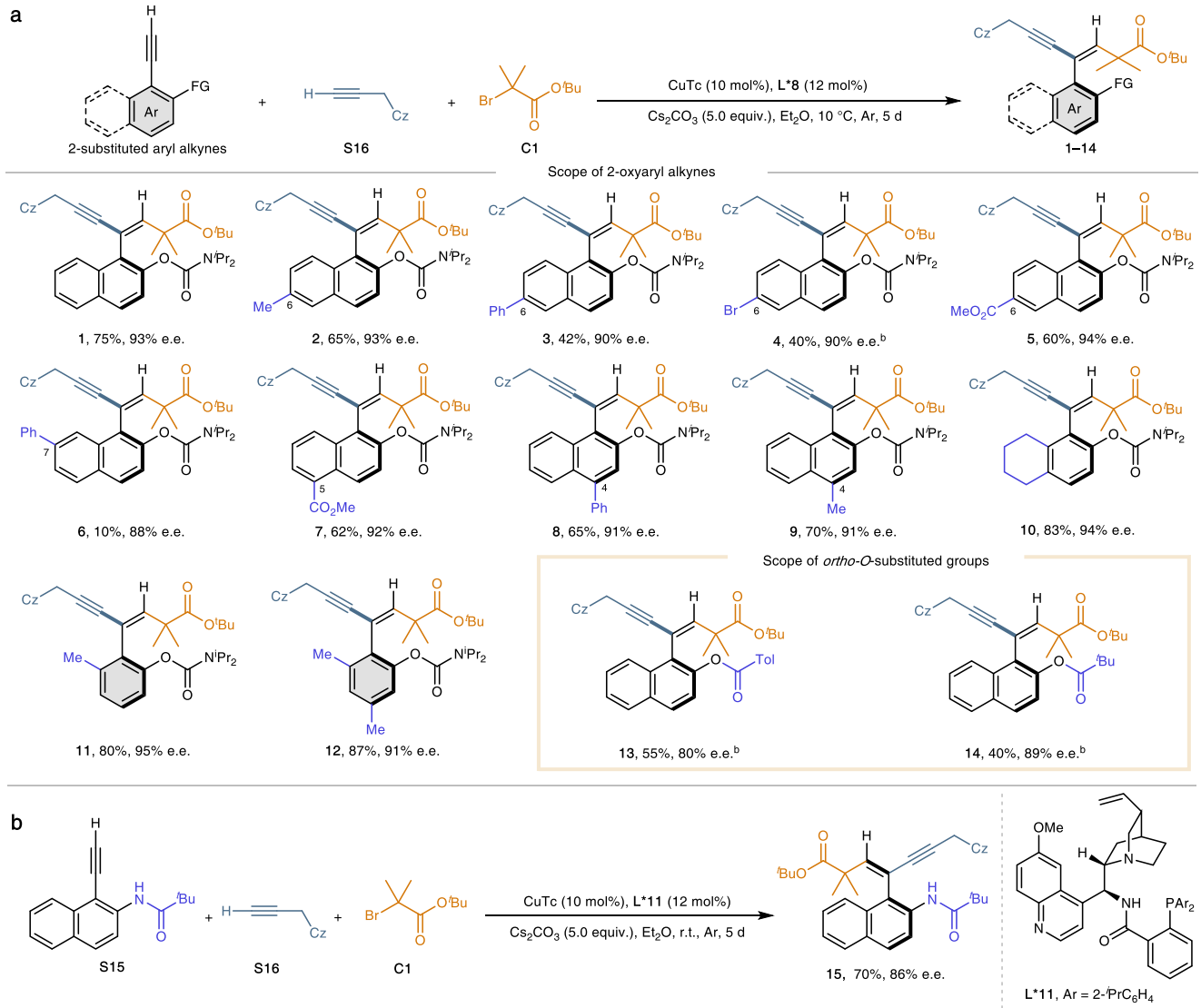

Fig. 2 | Substrate scope for 2-substituted aryl alkynes. a Substrate scope for 2-oxyaryl alkynes. Standard reaction conditions: 2-oxyaryl alkynes (2.0 equiv.), **C1** (2.0 equiv.), **S16** (0.20 mmol, 1.0 equiv.), CuTc (10 mol%), **L*8** (12 mol%), and Cs_2CO_3 (5.0 equiv.) in Et_2O (4.0 mL) at 10 °C for 5 d under argon. **b** *ortho-N*-substituted group. Standard reaction conditions: 2-aminoaryl alkyne **S15** (2.0 equiv.), **C1** (2.0 equiv.), **S16** (0.20 mmol, 1.0 equiv.), CuTc (10 mol%), **L*11** (12 mol%), and Cs_2CO_3 (5.0 equiv.) in Et_2O (4.0 mL) at r.t. for 5 d under argon. [b]Conducted at r.t. Isolated yield was shown; E.e. values were based on chiral HPLC analysis; FG functional group, Tol tolyl, Me methyl.

substrate to give the desired product in 40% yield with 84% e.e. These results demonstrated the importance of radical polarity to achieve asymmetric multicomponent process involving two similar terminal aryl alkynes with high chemo-, regio-, and stereoselectivity.

Synthetic utility

To demonstrate the synthetic potential of these axially chiral 1,3-enynes products, we first carried out gram-scale reactions with 2-oxyaryl alkyne substrate **S1** (Fig. 4a) and still obtained good yield and excellent enantioselectivity (1.96 g, 61% yield, and 92% e.e.). Next, we examined their thermal stability and observed marginal racemization up to 70 °C (see Supplementary Table 9 for more details). As is well known, axially chiral styrene compounds have proven to be a valuable chiral backbone for developing chiral catalysts or ligands in asymmetric catalysis[59,64,77,110–113]. To our delight, product **1** could be efficiently converted to corresponding triflate **34** in 41% overall yield with 92% e.e. (Fig. 4b), which has the potential to be a valuable partner in transition metal-catalyzed coupling reactions for constructing variety of axially chiral 1,3-enyne building blocks. Likewise, the configurational stability of product **33** was examined, and only marginal racemization was observed up to 80 °C (see Supplementary Table 10 for more details). The trivalent phosphine-based **35**, of which had the potential for asymmetric catalysis, could be easily synthesized by Ni-catalyzed coupling of **34** with Ph_2PH at 80 °C in 65% yield and 91% e.e. (Fig. 4c, left)[114]. Furthermore, Pd-catalyzed coupling of **34** with $Ph_2P(O)H$ at 80 °C provided the diphenyl phosphine oxide product **36** in a moderate yield with 90% e.e. (Fig. 4c, right)[115]. In addition, the absolute structure of product **1b** (Fig. 4b, and also see Supplementary Fig. 1) was determined to be *Ra* by X-ray structural analysis. Finally, we performed a preliminary investigation on the application of axially chiral compounds **35** and **36** as ligand in the Pd-catalyzed asymmetric cross-coupling[116]. As shown in Fig. 4d, diphenylphosphine **35** could catalyze the Suzuki–Miyaura cross-coupling of **37** and **38** as a potential ligand, affording the coupling product **39** with moderate yield and enantioselectivity, while diphenyl phosphine oxide **36** failed to afford the coupling product. These results demonstrate that the axially chiral 1,3-enyne scaffolds are promising for developing a new class of chiral monophosphine ligand.

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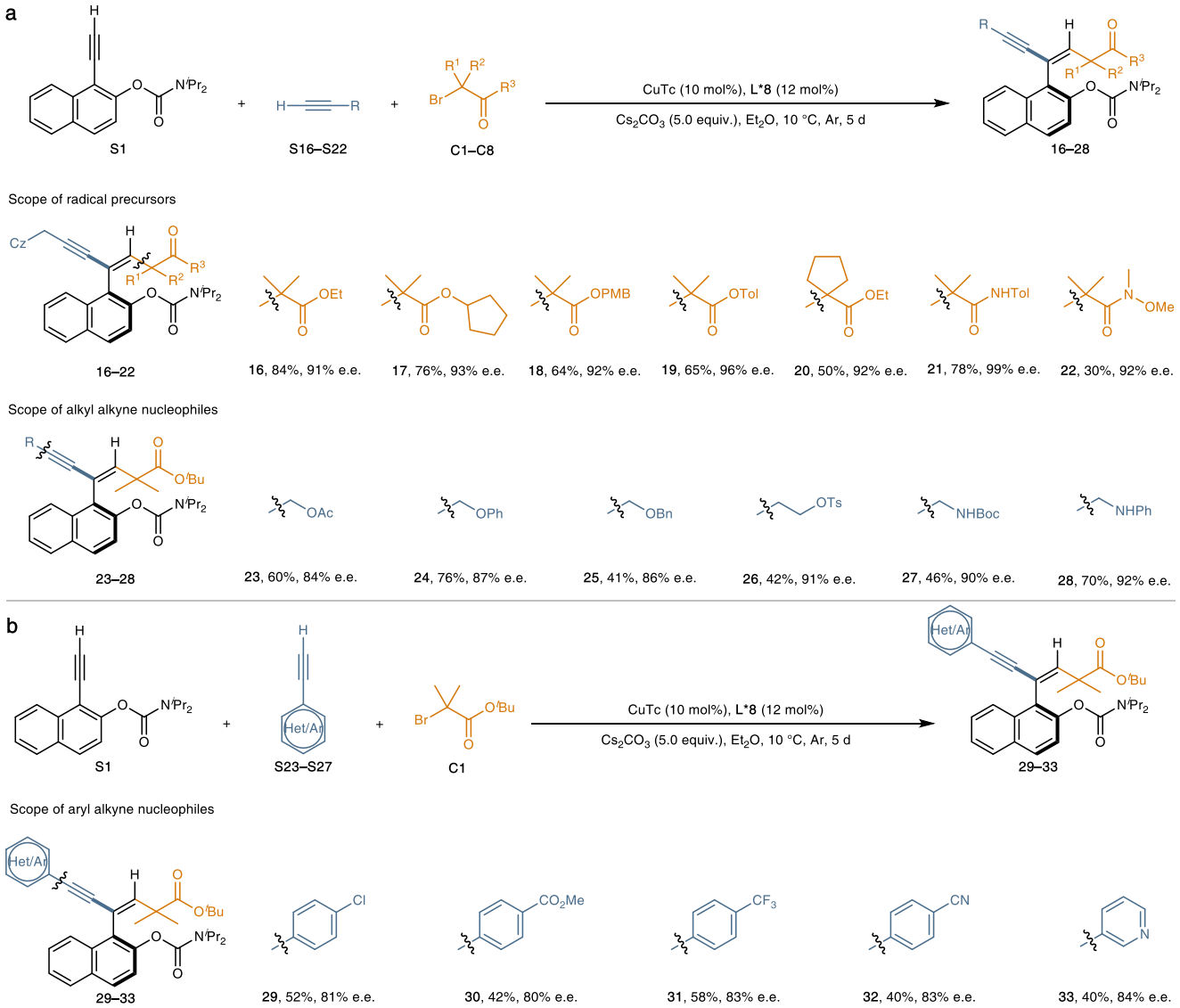

Fig. 3 | Substrate scope for radical precursors and alkyne nucleophiles. a Scope of radical precursors and alkyl alkyne nucleophiles. Standard reaction conditions: **S1** (2.0 equiv.), **S16–22** (0.20 mmol, 1.0 equiv.), radical precursor **C1–8** (2.0 equiv.), CuTc (10 mol%), **L*8** (12 mol%), and Cs_2CO_3 (5.0 equiv.) in Et_2O (4.0 mL) at 10 °C for 5 d under argon. **b** Scope of aryl alkyne nucleophiles. Standard reaction conditions: **S1** (2.0 equiv.), **S23–27** (0.20 mmol, 1.0 equiv.), **C1** (2.0 equiv.), CuTc (10 mol%), **L*8** (12 mol%), and Cs_2CO_3 (5.0 equiv.) in Et_2O (4.0 mL) at 10 °C for 5 d under argon. Isolated yield was shown; E.e. values were based on chiral HPLC analysis. Et ethyl, PMB 4-methoxybenzyl, Ac acetyl, Bn benzyl, Ts *p*-toluenesulfonyl, Ph phenyl, Boc *t*-butoxycarbonyl.

Mechanistic investigations

Control experiments conducted in the absence of the copper salt, chiral ligand, or base additive confirmed that all of these components were indispensable for the reaction (see Supplementary Table 11 for more details). The preliminary results of deprotonation experiments suggested that the less steric alkyl alkyne **S16** was consumed more rapidly than **S1** (see Supplementary Figs. 2 and 3), which might probably indicate the sterically bulky Cu^{I}**L*8** complex would favor deprotonation of less steric alkyne (Fig. 5c). In the presence of either BHT or TEMPO, the reaction was completely inhibited (Fig. 5a). Additionally, the BHT-trapped product **40** was isolated in 77% yield and the TEMPO adducts could be detected by high-resolution mass spectrometry (Fig. 5a, and also see Supplementary Fig. 6). Moreover, introducing an additional radical trapper, such as phenyl diselenide, resulted in the formation of vinyl radical trapped product **41** in 99% yield with 0% e.e. (Fig. 5a)[82]. These radical inhibition experiment results indicated the formation of an alkyl radical, which preferentially added to aryl alkynes **S1**, generating the conjugation-stabilized vinyl radical **IV** (Fig. 5c). An additional control experiment with alkenyl bromide **1″** failed to produce any product **1** under the standard conditions (Fig. 5b), indicating that a tandem atom-transfer radical addition/cross-coupling reaction pathway[21] is unlikely.

Based on these results as well as previous reports[90–92,98–103], we propose a plausible reaction mechanism, as shown in Fig. 5c. Copper(I) salt first coordinated with **L*8** to form the catalytically active species Cu^{I}**L*8**, entering the catalytic cycle. Then, complex Cu^{I}**L*8** selectively reacted with smaller-sized terminal alkyne **S-R^1** to generate the less steric Cu^{I}**L*8**–acetylide complex **I-R^1** in the presence of a base[91]. Afterwards, complex **I-R^1** underwent single-electron transfer (SET)[98] with alkyl bromide, giving rise to the Cu^{II}**L*8**–acetylide complex **II-R^1** and alkyl radical **III**. The following selectively intermolecular addition of **III** to the triple bond of alkyne **S-Ar** afforded the conjugation-stabilized vinyl radical **IV**[22]. Next, radical **IV** interacted with complex **II-R^1** to deliver the desired axially chiral 1,3-enyne products **1–33** and regenerated the Cu^{I}**L*8** complex in the presence of the highly sterically demanded ligand **L*8**. However, we do not have enough evidence to support the proposed process with excellent control of chemo-, regio-, and stereoselectivity and are currently performing more experimental and theoretical studies to disclose the detailed mechanism.

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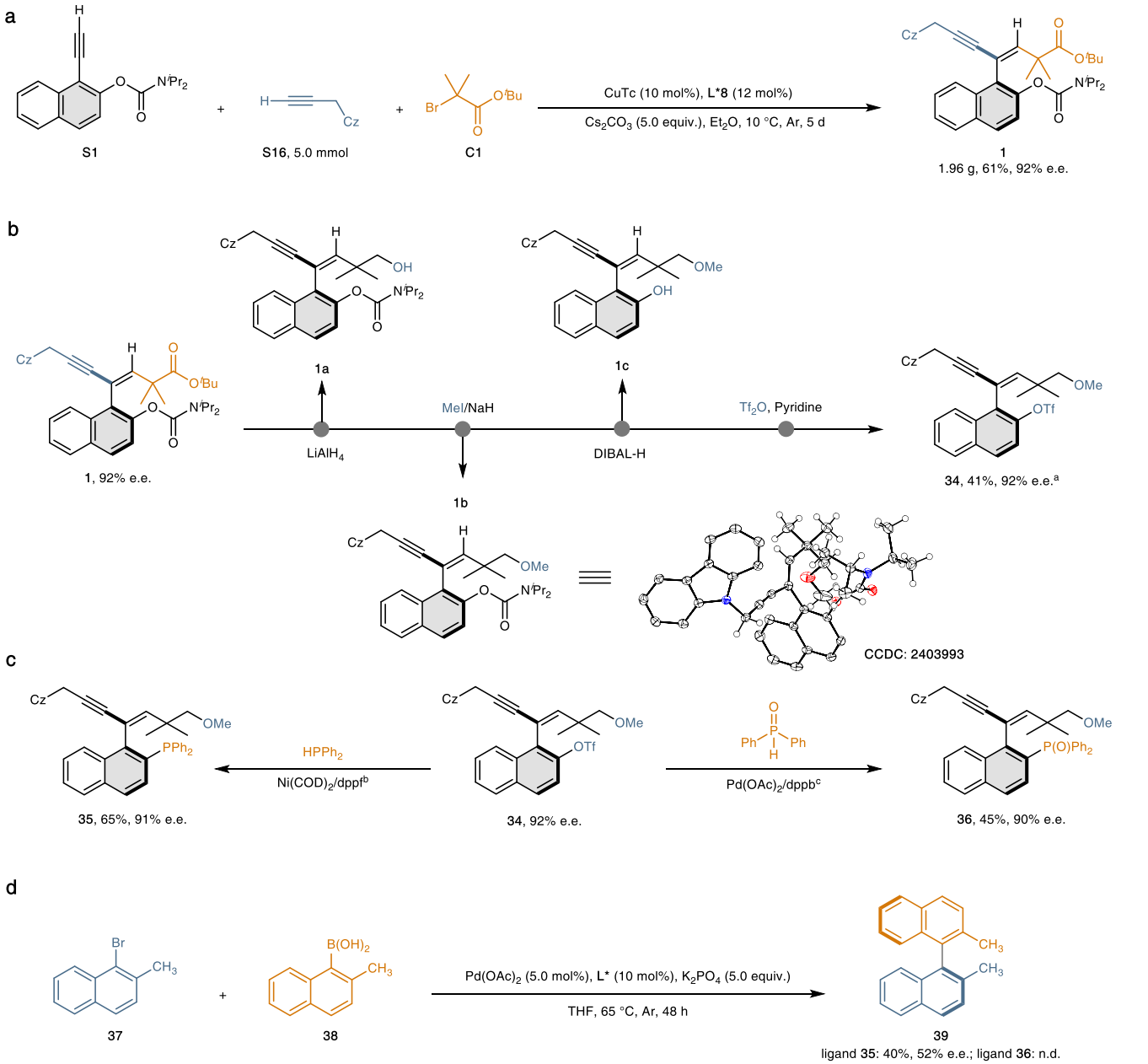

Fig. 4 | Synthetic utility for the construction of valuable axially chiral reagents. **a** Gram-scale reactions. **b**, **c** Transformation of enantioenriched axially chiral 1,3-enynes. **d** Chiral styrenes **35** and **36** as potential ligand in the Pd-catalyzed asymmetric cross-coupling. [a]Conditions: (i) $LiAlH_4$, THF, 0 °C, Ar, 4 h; (ii) MeI, NaH, THF, 0 °C, Ar, 4 h; (iii) DIBAL-H, DCM, –78 °C to r.t., Ar, 4 h; (iv) Tf_2O, pyridine, DCM, 0 °C to r.t., Ar, 4 h. [b]Conditions for **35**: $Ni(COD)_2$, dppf, $HPPh_2$, Na_2CO_3, 1,4-dioxane, 80 °C, Ar, 3 d. [c]Conditions for **36**: $Pd(OAc)_2$, dppb, $HP(O)Ph_2$, DIPEA, DMSO, 80 °C, Ar, 3 d. $LiAlH_4$ lithium aluminum hydride, THF tetrahydrofuran, DCM dichloromethane, DMSO dimethyl sulfoxide, COD 1,5-cyclooctadiene, DIBAL-H diisobutylaluminium hydride, dppf 1,1′-bis(diphenylphosphino)ferrocene, dppb 1,4-bis(diphenylphosphino)butane, DIPEA *N,N*-diisopropylethylamine, $HPPh_2$ diphenylphosphine, $HP(O)Ph_2$ diphenylphosphine oxide.

Discussion

In sum, we have demonstrated a three-component asymmetric radical 1,2-carboalkynylation with two different terminal alkynes and diverse alkyl radical precursors, which could successfully access axially chiral 1,3-enynes with excellent chemo-, regio-, and stereoselectivity under copper catalysis. The key to success lies not only in using the sterically bulky chiral multidentate anionic *N,N,P*-ligand but also in modulating alkynes with significantly different electronic properties to tune selectivity. This process features good substrate scope and functional group tolerance of terminal alkynes and radical precursors and readily affords an abundance of valuable enantioenriched axially chiral 1,3-enynes, thus providing a robust platform for expedient access to a myriad of chiral styrene building blocks. These results highlight the great potential of strategically devised multidentate anionic ligands for controlling the asymmetric multicomponent radical reactions with excellent selectivity.

Methods

Representative procedure for axially chiral 1,3-enynes

An oven-dried resealable Schlenk tube equipped with a magnetic stir bar was charged with 2-substituted aryl alkynes (0.40 mmol, 2.0 equiv.), alkyne nucleophiles (0.20 mmol, 1.0 equiv.), CuTc (3.8 mg, 0.02 mmol, 10 mol%), **L*8** (17.6 mg, 0.024 mmol, 12 mol%), and anhydrous Cs_2CO_3 (325.8 mg, 1.00 mmol, 5.0 equiv.). The tube was

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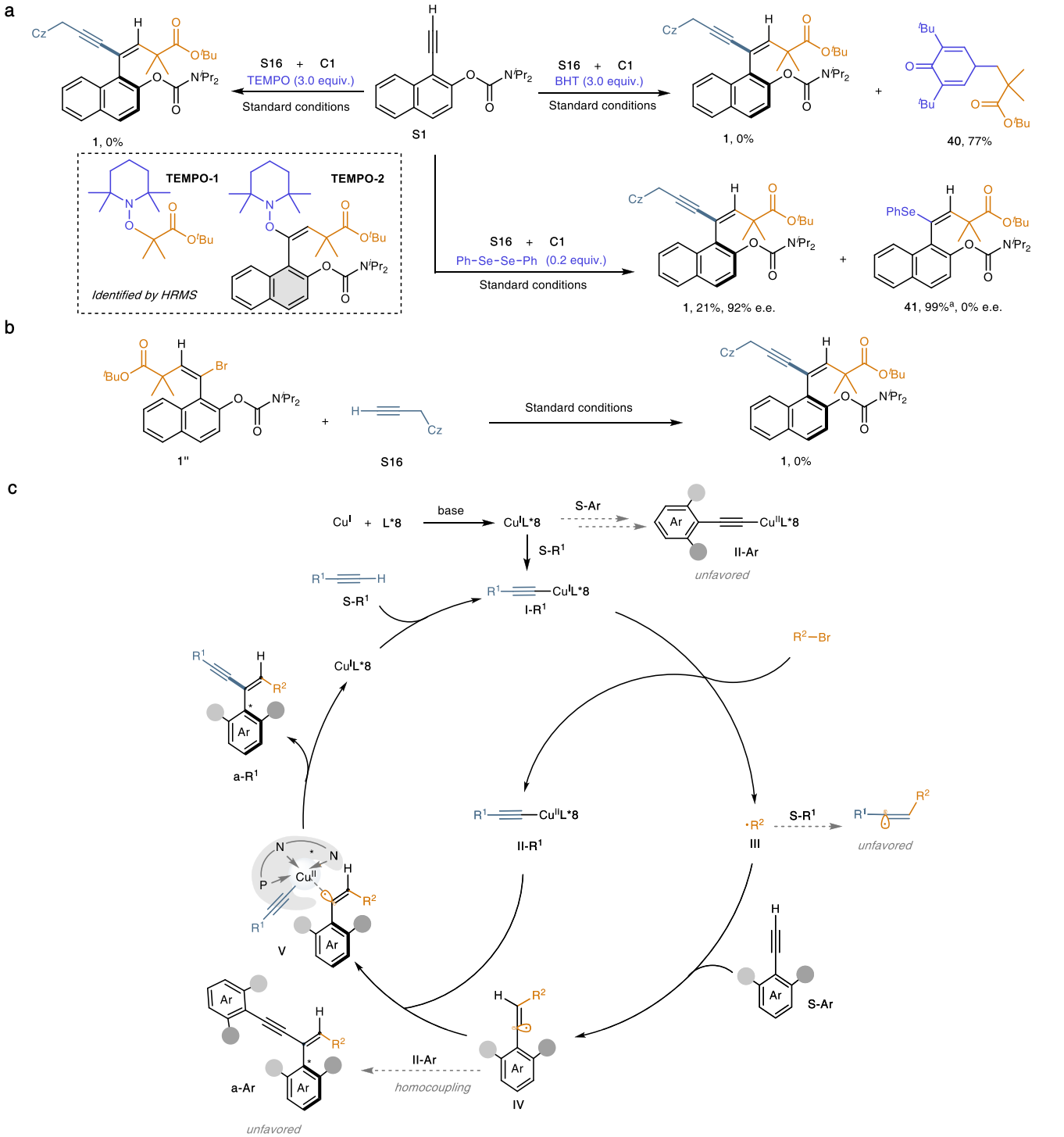

Fig. 5 | Mechanistic experiments and proposal. a Radical inhibition experiments with BHT, TEMPO, and phenyl diselenide. **b** Control experiments of vinyl bromide with **S16**. **c** Mechanistic proposal for the formation of axially chiral 1,3-enynes. [a]The yield of **41** was calculated based on the amount of phenyl diselenide. BHT butylated hydroxytoluene, TEMPO 2,2,6,6-tetramethyl-1-piperinedinyloxy.

evacuated and backfilled with argon three times. Then Et_2O (4.0 mL) was added by syringe under argon atmosphere. Finally, radical precursor (0.40 mmol, 2.0 equiv.) was added into the mixture and the reaction mixture was stirred at 10 °C for 5 d. Upon completion of the reaction (monitored by TLC), the reaction mixture was filtered through a short pad of Celite and washed with EtOAc. The filtrate was concentrated to afford the crude product, which was purified by column chromatography on silica gel to afford the desired product.

Data availability

All data are available in the main text and Supplementary Information and also available from the corresponding author upon request. Crystallographic data for the structures reported in this Article have been deposited at the Cambridge Crystallographic Data Centre, under deposition numbers CCDC 2403993 (**1b**) [https://doi.org/10.5517/ccdc.csd.cc2lpk51]. Copies of the data can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures/.

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Author contributions

J.-Q.B. and J.-B.T. designed the experiments and analyzed the data. J.-Q.B., L.Q., L.-W.F., J.F., Y.-F.C., Y.-F.Z., P.-F.W. and J.-B.T. performed the experiments. Q.S., Z.-L.L., Q.-S.G., P.Y., J.-B.T. and X.-Y.L. discussed the results and wrote the manuscript. J.-B.T. and X.-Y.L. conceived and supervised the project.

Competing interests

The authors declare no competing interests.

Additional information

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